

Metronidazole in the treatment of non-specific vaginitis (NSV)

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SUMMARY In a large multicentre study of 429 patients with the usual signs and symptoms of non-specific vaginitis (NSV), we studied the effect of different doses of metronidazole. The patients were divided into five treatment groups as follows: group A was given 400 mg metronidazole three times daily for seven days, group B 2000 mg as a single dose, group C 2000 mg on days 1 and 2, group D 2000 mg on days 1 and 3, and group E was given 1200 mg metronidazole once daily for five days. At follow up examination four weeks from the start of treatment, patients in groups D and E showed the best clinical results with cure rates of 94·0% and 93·6% respectively. In addition the rate of reisolation of *Gardnerella vaginalis* was lowest in group D. We therefore recommend metronidazole 2000 mg on days 1 and 3 as routine treatment for non-specific or vaginitis associated with gardnerella.

Introduction

Since the initial clinical report of Gardner and Dukes in 1955,¹ non-specific vaginitis (NSV) has been recognised as a clinical entity. It has been described under different names and at present the condition is most commonly called bacterial vaginosis² or vaginitis associated with gardnerella.³ It is probably related to the isolation of *Gardnerella vaginalis*, but other micro-organisms such as different anaerobic bacteria and so called comma shaped rods³ may be involved in the pathogenesis of the condition. There seems, however, to be a definite clinical condition, which is characterised by the following criteria: homogeneous, non-adherent vaginal discharge; pH of vaginal discharge >4·5-5·0; presence of clue cells in the discharge; amine-like smell after addition of 10% potassium hydroxide to the discharge. The clinical diagnosis of NSV requires that at least three of these criteria are present,² and *G vaginalis* can be cultured from vaginal material from most patients with NSV.^{2,3}

The vaginal use of sulpha creams was initially considered suitable treatment for NSV,¹ but since the

studies of Pheifer *et al*,⁴ Balsdon *et al*,⁵ and Malouf *et al*,⁶ metronidazole is now considered the drug of choice for NSV. This paper reports the results of a multicentre study in which patients were treated with different doses of metronidazole over different periods of time.

Patients, materials, and methods

We studied 429 patients with a clinical diagnosis of NSV based on the presence of at least three of the four clinical criteria cited above. Material from the vagina was sent to the laboratory in Stuart's transport medium and cultured for *G vaginalis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Candida albicans*. *G vaginalis* was identified by the method described by Shaw *et al*⁷; other bacteria were identified by routine laboratory procedures. Samples were also taken from some patients for isolation of anaerobic microbes. The amine test was performed by adding 10% potassium hydroxide to a sample of vaginal discharge, and the vaginal pH was measured by inserting a piece of pH paper into the vagina using a speculum. Clue cells were examined by microscopy after adding 0·9% saline to the vaginal discharge. Patients with positive cultures for *N gonorrhoeae* or *T vaginalis* were excluded from the study.

The patients were divided into five different treatment groups and given metronidazole as

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Accepted for publication 13 September 1983

follows: group A (n = 97) 400 mg three times daily for seven days; group B (n = 83) 2000 mg as a single dose; group C (n = 84) 2000 mg on days 1 and 2; group D (n = 85) 2000 mg on days 1 and 3; and group E (n = 80) 1200 mg once daily for five days. Four weeks after the start of treatment the patients were reassessed, and cultures and tests performed as at the first attendance. Sexual partners were given the same treatment as the patients. At follow up the patients were assessed as cured or not by the examining doctor according to the criteria for NSV. They were also asked to state whether they considered themselves cured or not.

All tests used in analysis of the results were one tailed.¹⁰ Differences with $p < 0.05$ were considered significant. The Wilcoxon rank sum test and signed midrank test were used to compare pH levels in, and changes within, treatment groups. Confidence intervals were calculated according to the Bernoulli-Wilcoxon procedure,⁸ and 95% confidence intervals of frequencies are calculated according to the theory of simple Bernoulli sequences.⁹ Fisher's exact test and McNemar's test were used to compare frequencies in, and changes within, treatment groups.

Results

Table I shows the ages of our patients and duration of their symptoms before treatment. The ages were similar in all groups, but the duration of symptoms varied as some groups included patients with symptoms of very long duration. In all five groups of patients, after treatment there were significant ($p < 0.01$) reductions in the frequency of malodour, the amount of vaginal discharge, and in the intensity of amine smell on addition of 10% potassium hydroxide (data not shown). Table II shows that there also was a significant ($p < 0.01$) reduction in the pH of the vaginal discharge in all groups. In table III the frequency of isolation of *G vaginalis* before and after treatment is shown. A significant reduction ($p < 0.01$) in isolation after treatment was found in all groups, being most evident in group D.

TABLE I Mean (range) ages and duration of symptoms of 429 patients with NSV

Group	Treatment with metronidazole	Ages in years	Days' duration of symptoms
A (n = 97)	400 mg thrice daily for 7 days	30 (17-49)	42 (7-2400)
B (n = 83)	2000 mg in a single dose	27 (17-57)	63 (2-1000)
C (n = 84)	2000 mg on days 1 and 2	30 (11-70)	42 (7-730)
D (n = 85)	2000 mg on days 1 and 3	28 (16-55)	63 (7-3600)
E (n = 80)	1200 mg once daily for 5 days	32 (17-52)	42 (14-42)

TABLE II Vaginal pH in 429 patients with NSV before and after treatment

Group	Treatment with metronidazole	Mean (SD) pH		Mean reduction
		Before	After	
A (n = 97)	400 mg thrice daily for 7 days	5.8 (0.1)	5.0 (0.2)	0.8 ($p < 0.01$)
B (n = 83)	2000 mg in a single dose	5.6 (0.1)	4.8 (0.1)	0.7 ($p < 0.01$)
C (n = 84)	2000 mg on days 1 and 2	5.6 (0.1)	4.7 (0.1)	0.9 ($p < 0.01$)
D (n = 85)	2000 mg on days 1 and 3	5.8 (0.1)	4.8 (0.1)	1.2 ($p < 0.01$)
E (n = 80)	1200 mg once daily for 5 days	5.8 (0.1)	4.7 (0.1)	1.1 ($p < 0.01$)

TABLE III Isolation of *G vaginalis* from 429 patients with NSV before and after treatment

Group	Treatment with metronidazole	No positive		Significance
		Before	After	
A (n = 97)	400 mg thrice daily for 7 days	90	15	($p < 0.01$)
B (n = 83)	2000 mg in a single dose	81	15	($p < 0.01$)
C (n = 84)	2000 mg on days 1 and 2	82	21	($p < 0.01$)
D (n = 85)	2000 mg on days 1 and 3	74	6	($p < 0.01$)
E (n = 80)	1200 mg once daily for 5 days	78	19	($p < 0.01$)
Total	429	405	76	($p < 0.01$)

Table IV shows the estimate of probability of the eradication of *G vaginalis* after treatment, as well as the 95% confidence interval estimate for that probability in each group. Again group D, in which patients were given 2000 mg metronidazole on days 1 and 3, showed the highest cure rate. Tables V and VI show the probability of the cure rate in each group, as estimated by the examining doctor and by the patient herself, and the estimate of the 95% confidence interval for each probability. Again

TABLE IV Probability of eradication of *G vaginalis* from 429 patients with NSV

Group	Treatment with metronidazole	% point estimate	95% confidence interval (%)
A (n = 97)	400 mg thrice daily for 7 days	82.4	73.3-89.6
B (n = 83)	2000 mg in a single dose	81.7	71.3-89.1
C (n = 84)	2000 mg on days 1 and 2	74.1	62.9-82.9
D (n = 85)	2000 mg on days 1 and 3	92.4	83.2-96.8
E (n = 80)	1200 mg once daily for 5 days	75.6	64.4-84.3

TABLE V Probability of cure rates in 429 patients with NSV as estimated by the doctor

Group	Treatment with metronidazole	% point estimate	95% confidence interval (%)
A (n=97)	400 mg thrice daily for 7 days	86.6	77.8-92.4
B (n=83)	2000 mg in a single dose	84.3	74.3-91.1
C (n=84)	2000 mg on days 1 and 2	81.2	70.9-88.5
D (n=85)	2000 mg on days 1 and 3	94.0	85.9-97.6
E (n=80)	1200 mg once daily for 5 days	93.6	85.0-97.6

TABLE VI Probability of cure rates in 429 patients with NSV as estimated by the patient

Group	Treatment with metronidazole	% point estimate	95% confidence interval (%)
A (n=97)	400 mg thrice daily for 7 days	80.4	70.9-87.5
B (n=83)	2000 mg in a single dose	80.7	71.3-88.3
C (n=84)	2000 mg on days 1 and 2	70.6	59.6-79.6
D (n=85)	2000 mg on days 1 and 3	89.2	79.9-94.6
E (n=80)	1200 mg once daily for 5 days	86.3	76.3-92.6

group D showed the highest cure rate, but this was only slightly better than in group E and not significantly better than in the other groups.

Side effects were few and did not cause any of the patients to stop the treatment. A few patients complained of a metallic taste, but nausea was no problem in any of the groups. Table VII shows the isolation rates of *C. albicans* before and after treatment. Patients in groups A and E, who were given the longest course of treatment, showed a significant ($p<0.01$) increase in isolations, which was not observed with shorter treatment regimens. In a

TABLE VII Isolation of *C. albicans* from 429 patients with NSV before and after treatment

Group	Treatment with metronidazole	No positive		Significance
		Before	After	
A (n=97)	400 mg thrice daily for 7 days	5	15	$p<0.01$
B (n=83)	2000 mg in a single dose	5	7	NS
C (n=84)	2000 mg on days 1 and 2	4	8	$p=0.09$
D (n=85)	2000 mg on days 1 and 3	6	4	NS
E (n=80)	1200 mg once daily for 5 days	3	13	$p<0.01$

smaller group, 60 patients from group E, vaginal material was cultured for anaerobic bacteria. A significant reduction ($p<0.01$) in the isolation rate was found after treatment (data not shown). The anaerobes most commonly cultured were *Bacteroides* species and anaerobic streptococci.

Discussion

There seems to be little doubt that metronidazole is the drug of choice for the treatment of NSV.^{4,6} As it is claimed to be a potentially dangerous drug,¹¹ as low a dosage in as short a time as possible to gain satisfactory results should be used. Recent pharmacokinetic studies¹² have shown that single oral doses of 1200-2000 mg of metronidazole can give plasma and urine concentrations that exceed the minimum inhibitory concentration (MIC) for some strains of *G. vaginalis*. The importance of this is uncertain, as acceptable results have been achieved with lower doses of metronidazole when MICs for *G. vaginalis* in the plasma were not obtained.^{4,5} The satisfactory clinical results in these studies probably show the effect of metronidazole on anaerobic microorganisms, which may play a part in NSV. Another factor that might be important is the effect of the metabolite of metronidazole, 2-hydroxy-metronidazole, and of the high concentration of it in the urine.¹²

In this study the regimens in which metronidazole was given at a dosage of 400 mg three times daily for seven days (group A), 2000 mg daily on days 1 and 3 (group D) and 1200 mg daily for five days (group E), all showed satisfactory clinical results with high cure rates. In the group of patients given 1200 mg metronidazole daily for five days (group E) the reduction in the isolation of *G. vaginalis* was significantly ($p<0.01$) lower than in the group given 2000 mg on days 1 and 3. Treatment for five or seven days was associated with significantly increased isolation of *C. albicans*, probably due to the effect on the vaginal "ecosystem" of microflora. The clinical significance of increased *C. albicans* isolation is uncertain, but it seems to indicate a shorter treatment time.

We conclude that treatment of NSV with metronidazole 2000 mg given in single doses on days 1 and 3 gives a high cure rate, has few side effects, and in most cases eradicates *G. vaginalis*. This regimen can be recommended as a routine treatment for non-specific vaginitis associated with gardnerella.

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